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REMARKS

Present Claims 2-4, 6, and 8-12 relate to methods for treating a dry eye, comprising ocular administration of an effective amount of a macrolide compound to a subject in need of the treatment of dry eye.

The inventor has surprisingly found that occular administration of a macrolide compound is effective for the treatment of dry eye. The cited reference contains no disclosure or suggestion of the presently claimed methods. Accordingly, these reference cannot affect the patentability of the present claims.

The rejection of Claims 2-12 [sic, Claims 2-4, 6, and 8-12] under 35 U.S.C. § 102(b) in view of U.S. Patent No. 5,770,607 (Honbo et al) is respectfully traversed. Honbo et al discloses aqueous eye drop suspensions of a tricyclo compound, including FK506, and their use for the treatment of vernal conjunctivitis as an autoimmune disease in the ophthalmic field. On page 3 of the Office Action, the position is taken that vernal conjunctivitis is another name for keratoconjunctivitis, and a printout of a page from www.my.webmd.com is cited as support for that assertion.

However, the referenced page from www.my.webmd.com does not support the equivalence of *vernal* conjunctivitis and keratoconjunctivitis. Instead, this web page only teaches that "*seasonal* conjunctivitis" and "keratoconjunctivitis, *vernal* (*i.e.*, *vernal* keratoconjunctivitis)" are synonymous. As is well known, the adjective "vernal" means "of, relating to, or occurring in the spring." See, the entry for "vernal" from Webster's Ninth New Collegiate Dictionary, Merriam-Webster, Springfield, MA, p. 1310 (1988) filed herewith.

In the case of "vernal conjunctivitis" and "vernal keratoconjunctivitis," the term "vernal" means that the condition is "a seasonal allergic disorder usually appearing during the spring or warm weather." See, page from www.my.webmd.com supplied by the Examiner.

Thus, to be precise, "vernal conjunctivitis" is a seasonal allergic diseases involving autoimmunity.

In sharp contrast, the term "dry eye" as used in the present invention is defined to mean "a condition wherein lacrimal fluid is less in amount or abnormal in quality, with or without the presence of corneal and conjunctival lesion (Yamada, M. et al., Folia Ophthalmol. Jpn., 43, 1289-1293 (1992))." *See*, page 1, lines 8-11, of the specification. Thus, the vernal conjunctivitis of <u>Honbo et al</u> is a very different disease from the dry eye, which is the target disease of the presently claimed methods.

Accordingly, <u>Honbo et al</u> does not disclose any method for treating dry eye or therapeutic effect on dry eye. Accordingly, this reference cannot anticipate the present claims.

Moreover, there is no teaching in <u>Honbo et al</u> which would suggest that administration of a macrolide compound would be useful for the treatment of dry eye. Accordingly, this reference cannot make the present claims obvious.

For these reasons, the rejection should be withdrawn.

Lastly, Applicant wishes to thank Examiner Azpuru for returning an initialed copy of the Form PTO 1449 filed with the Information Disclosure Statement filed on August 7, 2003. However, Applicant notes that References AA, AB, AC, AD, and AY were not initialed.

U.S. Application No.: 09/926,411

communication from the PTO.

Reply to Office Action dated January 15, 2004

Since Reference AB was discussed in the Office Action, Applicant presumes that the failure to initial References AA, AB, AC, AD, and AY was simply a clerical error. Accordingly, Applicant is submitting another copy of the Form PTO 1449 filed with the Information Disclosure Statement filed on August 7, 2003, so the Examiner can place his initials next to References AA, AB, AC, AD, and AY and return a copy of the initialed form with the next

Applicant submits that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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Made in the United States of America

: the male intromittent organ of any of various invertebrates 2 a something that borders, limits, or bounds: as (1): an outer margin of an object or structural part (2): the edge of roof covering (as tiling) projecting over the gable of a roof (3) Brit: the shoulder of a foad b: BRINK, THRESHOLD (a country on the \sim of destruction—Archibald MacLeish)

²verge vi.verged; verg-ing (1787) 1: to be contiguous 2: to be on the verge or border

verge vi verged; verg-ing [L vergere to bend, incline — more at wrench] (1610) 1 a of the sun: to incline toward the horizon: SINK b: to move or extend in some direction or toward some condition 2: to be in transition or change verger \'vər-jər\ n (15c) 1 chiefly Brit: an attendant that carries a verge (as before a bishop or justice) 2: a church official who keeps

ve-rid-i-cal \ve-rid-i-kel\ adj [L veridicus, fr. verus true + dicere to say more at VERY, DICTION] (1653) 1: TRUTHFUL, VERACIOUS 2: not

veridical \va-'rid-i-kal\ adj | L veridicus, fr. verus true + dicere to say — more at VERY, DICTION] (1653) 1: TRUTHFUL, VERACIOUS 2: not illusory: GENUINE — veridi-cali-ty \-,rid-a-'kal-at-\(\bar{e}\) n — veridi-cali-ty \-,rid-a-'kal-at-\(\bar{e}\) n — veridi-cali-ty \-,veri-fi-able \(\ver-a-\), fi-a-bal\ adj (1593): capable of being verified — veri-fi-fiable \(\ver-a-\), fi-a-bal\ adj (1593): the act or process of verifying: the state of being verified n — veri-fi-able-ness n veri-fi-ca-tion \(\ver-a-\), ver-a-fa-'k\(\bar{e}\)-shann n (1523): the act or process of verifying: the state of being verified verifien, fr. MF verifier, fr. ML verificare, fr. L verus true — more at VERY] (14c) 1: to confirm or substantiate in law by oath 2: to establish the truth, accuracy, or reality of syn see CONFIRM — veri-fi-er\(\ver-a-\), fi-abl \(\ver\) ver-a-l\(\ver\) ver-a-l\(\ver\) adv [ME verraily, fr. verray very] (14c) 1: in truth : CERTAINLY 2: TRULY, CONFIDENTLY veri-sim-i-lar \(\ver-a-\), ver-a-'sim-(a-)lar\(\ver-a\) adj [L verisimilis] (1681) 1: having the appearance of truth: PROBABLE 2: depicting realism (as in art or literature) — veri-sim-i-lar-ly adv veri-si-mil-i-tude \(\ver-sa-\)-mil-a-1(y)\(\ver\) dd\(\ver\) n [L verisimilitudo, fr. verisimilis verisimilar, fr. veri similis like the truth] (1603) 1: the quality or state of being verisimilar 2: something verisimilar — veri-si-mil-i-tu-di-nous \(\ver\)-mil-a-1(y)\(\ver\) dd-nas, \(\ver\)-nas\(\ad\) adj verism \(\ver\)-i(x)-m, \(\ver\)-nas\(\ad\) opera — veri-si-visi-tu-di-nous \(\ver\)-in-a-s\(\ad\) adj

verism \vi(\partial)r-\partialz-\partials, \vertials \(\text{1892} \): artistic use of contemporary everyday material in preference to the heroic or legendary esp. in grand opera — verist \-\partials \(\text{n} \) nor adj — veristic \vi(\partial)r-\text{is-tik}, \(\text{ve0} \) r-\\ adj \\
veristic \vertials \vertials \\ \text{ver-ta-ta-bal} \) adj \\
(ME. \text{ fr. MF, fr. verite} \) (15c): being in fact the thing named and not false, unreal, or imaginary — often used to stress the aptness of a metaphor \(\alpha \pi \) mountain of references \(\text{syn} \) see AUTHENTIC — veri-\text{ta-ble-ness } n — veri-\text{ta-bly} \\ \vertie\vertials \\ \text{log} \) (1966): the art or technique of filming (as a motion picture) so as to convey candid realism \\
ver-\text{i-tix} \\ \vertie-\vertials \\ n \ [F, \text{truth, fr. MF verite} \) (1966): the art or technique of filming (as a motion picture) so as to convey candid realism \\
ver-\text{i-tas, fr. verus true} \) (14c) 1: the quality or state of being true or real 2: something (as a statement) that is true; \(\ext{esp} : a \) fundamental and inevitably true value \(\text{such eternal verities} \) as honor, love, and patriotism \(\text{3: the quality or state of being truthful or honest \(\text{the king-becoming graces, as justice, } \simple \simple \text{Shak.} \)

'er-\text{juice \vertical var-\text{jus} \n [ME verjus, fr. MF, fr. vert \(\text{jus.} \) lit., green \(\text{juice} \) (14c) 1: the sour \(\text{juice of crab apples or of unripe fruit (as grapes or apples); \(also : \text{ an acid liquor made from verjuice} \) 2: acidity of disposition or manner \(\text{loss} \) an acid liquor made from verjuice 2: acidity of disposition or manner \(\text{loss} \) 1 \\
\text{loss} \vert

'er-meil n [MF, fr. vermeil, adj. — more at VERMILION] (15c) 1 \'vər-məl, -māl\: VERMILION 2 \ve(ə)r-mā\: gilded silver — vermeil adj ermi-comb form [NL, fr. LL, fr. L vermis — more at worm]: worm

(vermiform)
er-mi-cel·li \,vər-mə-'chel-ë, -'sel-\ n [It, fr. pl. of vermicello. dim. of verme worm, fr. L vermis] (1669): pasta made in long solid strings smaller in diameter than spaghetti
er-mi-cide \'vər-mə-,sīd\ n (1849): an agent that destroys worms
er-mi-cide \'vər-mi-,sīd\ n (1849): an agent that destroys worms
er-mi-cide \'vər-mi-yə-lər\ adj [NL vermicularis, fr. L vermiculus, dim. of vermis] (1672) 1 a: resembling a worm in form or motion b
: VERMICULATE 2: of, relating to, or caused by worms
er-mi-cide \-lət\ or ver-mi-cid-lated \-,lāt-əd\ adj [L vermiculatus, fr. vermicula] (1605) 1 a: VERMIFORM b: marked with irregular fine lines or with wavy impressed lines (a ~ nut) 2: TORTUOUS, INVOLUTE
3: full of worms: worm-eaten — ver-mi-cid-lation \-, mik-yə-'lā-shən\ n

ner-mic-u-lite \(\,\)\var-'mik-yə-,lit\ n [L vermiculus little worm] (1824): any of various micaceous minerals that are hydrous silicates resulting usu. from expansion of the granules of mica at high temperatures to give a lightweight highly water-absorbent material er-mi-form\'var-mə-,form\ adj [NL vermiformis, fr. vermi- + -formis form] (ca. 1730): resembling a worm in shape ermiform appendix n (ca. 1778): a narrow blind tube usu. about three or four inches long that extends from the cecum in the lower right and part of the abdomen

nand part of the abdomen

nand part of the abdomen ar-mi-fuge \var-ma-fyüj\ adj [prob. fr. (assumed) NL vermifugus, fr. ermi-tuge \var-ma-fyüj\ adj [prob. fr. (assumed) NL vermifugus, fr. ermi- + L fugare to put to flight — more at FUGE] (1697): serving to testroy or expel parasitic worms: ANTHELMINTIC — vermifuge n r-mil-ion also ver-mil-lion \var-mil-yan\ n [ME vermifuon, fr. OF rermeillon, fr. vermeil, adj., bright red, vermilion, fr. LL vermiculus ermes, fr. L, little worm] (14c) 1: a bright red pigment consisting of nercuric sulfide; broadly: any of various red pigments 2: a variable color averaging a vivid reddish orange

color averaging a vivid reddish orange r-min \vər-mən\ n. pl vermin [ME, fr. MF, fr. (assumed) L vermin-vermen worm; akin to L vermis worm — more at worm] (14c) 1 a small common harmful or objectionable animals (as lice or fleas) that re difficult to control b: birds and mammals that prey on game 2

re difficult to control b: birds and mammals that prey on game 2 an offensive person raminous \'vər-mə-nə\ adj (1616) 1: consisting of or being vermin NOXIOUS 2: forming a breeding place for or infested by vermin FILTHY (~ garbage) 3: caused by vermin (~ disease) ramouth \vər-muth\ n [F vermout, fr. G wermut wormwood, fr. OHG rermuota — more at workmwood] (1806): a dry or sweet aperitif wine avored with aromatic herbs and often used in mixed drinks er-nac-u-lar \və(r)-'nak-yə-lər\ adj [L vernaculus native, fr. verna slave orn in his master's house, native] (1601) 1 a: using a language or ialect native to a region or country rather than a literary, cultured, or

foreign language b: of, relating to, or being a nonstandard or substandard language or dialect of a place, region, or country c: of relating to, or being the normal spoken form of a language 2: applied to a plant or animal in the common native speech as distinguished from the Latin nomenclature of scientific classification 3: of, relating to or characteristic of a period, place, or group; esp: of, relating to or characteristic of a period, place, or group; esp: of, relating to or characteristic of a period, place, or group; esp: of, relating to or characteristic of a period or place — ver-nac-u-lar-ly adv

²vernacular n (1706) 1: a vernacular language, expression, or mode of expression 2: the mode of expression of a group or class 3: a vernacular name of a plant or animal vernacular ism (və/n)-'nak-yə-lə-riz-əm(n (ca. 1846): a vernacular

word or idiom

ver-nac-u-iar-ism (va(r)-nak-ya-1a-riz-am) n (ca. 1640); a vernacular word or idiom ver-nal \'varn-2\' adj [L vernalis, alter. of vernus, fr. ver spring; akin to Gk ear spring] (1534) 1: of, relating to, or occurring in the spring (equinox) (~ sunshine) 2: fresh or new like the spring; also: YOUTH FUL—ver-nal-ly \-?\-2\ adv ver-nal-iza-tion \, varn-2\-2\-2\ a-\ z\ ashan\ n (ca. 1932): the act or process of hastening the flowering and fruiting of plants by treating seeds, bulbs, or seedlings so as to induce a shortening of the vegetative period — ver-nal-iza \'varn-2\-\frac{1}{12}\varphi v ver-na-tion \(\lambda\)\var-\na-shan\ n [NL vernation-, vernatio, fr. L vernation pp. of vernare to behave as in spring, fr. vernus vernal] (1793): the arrangement of foliage leaves within the bud

Ver-ner's law \, ve(\alpha)r-narz-\ n [Karl A. Verner] (ca. 1892): a statement in historical linguistics: in medial or final position in voiced environments and when the immediately preceding vowel did not bear the principal accent in Proto-Indo-European, the Proto-Germanic voiceless stops p, t, and k and the Proto-Germanic voiceless fricatives f, b, and x are proto-Indo-European s became the voiced fricatives b, \(\delta\), g, and z represented in various recorded Germanic languages by b, d, g, and z represented in various recorded Germanic languages by b, d, g.

and z represented in various recorded Germanic languages by b, d, g, and r
verni-cle or verna-cle \'vər-ni-kəl\ n [ME vernicle, fr. MF veronique, vernicle, fr. ML veronica] (14c): \(^2\)veronicle, fr. MF veronique, vernicle, fr. ML veronica] (14c): \(^2\)veronicle, fr. MF veronique, vernicle, fr. ML veronica] (12c): \(^2\)veronicle, fr. MF veronique, fr. MF veronica distance in the speed or course or controlling the attitude — called also vernier engine for making fine adjustments in the speed or course or controlling the attitude — called also vernier engine for a realled also vernier engine for a vernier adje (1788): having or comprising a vernier vernier called in (1876): a measuring device that consists of a main scale with a fixed jaw and a sliding jaw with an attached vernier vernis-sage \(^2\)ver-in-'-säzh\ n [F, day before an exhibition opens reserved for artists to varnish and put finishing touches to their paintings, lit. varnishing, fr. vernis varnish — more at varnish] (1926): a private showing or preview of an art exhibition for proper or preview of an art exhibition or pr

ver-ru-ca $\forall v$ -'rü-kə $\forall n$, pl-cae $\forall (1)$ kē, -,kî, -,sī $\forall [L - more at wart]$ (1565) 1: a wart or warty skin lesion 2: a warty elevation on a plant or animal surface verruca vul·ga·ris \-,vəl-'gar-əs, -'ger-\ n [NL, lit., common verruca] (ca. 1903): WART la

ver-sucose \v2-'rū-kōs\ adj (1686): covered with warty elevations ver-sal \v2-'rū-kōs\ adj (short for universal] archaic (1592): ENTIRE. WHOLE (as pale as any clout in the ~ world —Shak.)

ver-sant \v2-s-²nt\ adj [L versant-, versans, prp. of versare, versari to turn, occupy oneself, meditate] (1645) 1 archaic: EXPERIENCED, PRACTICED 2: CONVERGANT.

TICED 2: CONVERSANT

*ver-sant \'vors-\angle n, ve(\alpha)r-\san\ n [F, fr. MF, fr. prp. of verser to turn. pour, fr. L versare to turn; fr. its shedding of water] (1851) 1: the slope of a side of a mountain chain 2: the general slope of a country INCLINATION

slope of a side of a mountain chain 2: the general slope of a country: INCLINATION

ver-sa-tile \'vər-sət-\], esp Brit -sə-til\ adj [F or L; F, fr. L versatilis turning easily, fr. versatus. pp. of versare to turn, fr. versus, pp. of vertere] (1605) 1: changing or fluctuating readily: VARIABLE (a \sigma disposition) 2: embracing a variety of subjects, fields, or skills; also: turning with ease from one thing to another 3 a (1): capable of turning forward or backward: REVERSIBLE (a \sigma toe of a bird) (2): capable of moving laterally and up and down (\sigma antennae) b of an anther: having many uses or applications (\sigma building material) — ver-sa-tile-ly \-\frac{1}{2}\-(1)\varepsilon_*, \tau\). [1]-\varepsilon_* (a. 1755): the quality or state of being versatile (a writer of great \sigma versatile (a writer of great \sigma versatile (a writer of great \sigma versus, pp. of vertere to turn — more at worth [bef. 12c) 1: a line of metrical writing 2 a (1): metrical language (2): metrical writing distinguished from poetry esp. by its lower level of intensity (3): poetrery b: POEM c: a body of metrical writing (as of a period or country) 3: STANZA 4: one of the short divisions into which a chapter of the Bible is traditionally divided

2verse vb versed; vers-ing [back-formation fr. versed, fr. L versatus, pp. of versar to be active, be occupied (in), pass, of versar to turn, fr. versus, pp. [1673): to familiarize by close association, study, or experience (versed himself in the theater)

verset \'vərs-ət, -et, vər-'set\ n [ME, fr. OF, dim. of vers verse] (13c)

versed himself in the theater